REMARKS

Claims 1-17 are pending in this application. The issues outstanding in this application are as follows:

- Claims 1-2 have been rejected under 35 U.S.C. 112, second paragraph, which the Examiner alleges that the claimed subject matter is indefinite.
- Claims 1-4 have been rejected under 35 U.S.C. 102(a), which the Examiner alleges that the claimed subject matter is anticipated by Kapur, V et al. (Microbial Path., 1993) and Kapur, V et al. (PNAS, 1993).
- Claims 1-4 have been rejected under 35 U.S.C. 102(b), which the Examiner alleges that the claimed subject matter is anticipated by Tai et al., or Hauser and Schlievert, or Gerlach et al.
- Claim 5 has been rejected under 35 U.S.C. 103(a), which the Examiner alleges that the claimed subject matter is unpatentable over Kapur, V. et al. (Microbial Path., 1993), Kapur, V et al., (PNAS, 1993) or Tai et al., or Hauser and Schlievert, or Gerlach et al., in view of Abe et al.
- Claims 6-17 have been rejected under 35 U.S.C. 103(a), which the Examiner alleges that the claimed subject matter is unpatentable over Fischetti et al., and Kehoe in view of Kapur, V. et al. (Microbial Path., 1993), Kapur, V et al., (PNAS, 1993) or Tai et al., or Hauser and Schlievert, or Gerlach et al., and in further view of Abe et al.

Applicants respectfully traverse the outstanding rejections and respectfully request reconsideration and withdrawal thereof in light of the remarks contained herein.

35 U.S.C. § 112

Claims 1 and 2 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully assert that Claims 1 and 2 are not indefinite.

The Office Action alleges that Claim 1 is vague and indefinite because it recites "in an amount sufficient to confer immunity to Group A streptococcal infection". Applicants assert that a vaccine is a preventative agent which acts by conferring immunity against a specific pathogen or class of pathogens. Therefore, there is no therapeutic amount of vaccine to be administered. Claim 1 uses the language "amount sufficient to confer immunity" to indicate the proper target

for vaccine dosage (See Declaration by Dr. Musser, paragraph 10). Claim 1 therefore instructs the skilled artisan that the vaccine must contain enough cysteine protease to invoke a protective immune response in the patient.

Applicants assert that it is not necessary to recite that the vaccine is "being administered to" in order to make the intended use functional. Applicants respectfully assert that the skilled artisan understands the term "vaccine" refers to the particular preparation intended for administration. For example, a skilled artisan, and even perhaps a layperson, would understand that a vial of smallpox or flu materials, which are used as immunization agents in humans, are "vaccines" without the necessity of reciting its intended use. Furthermore, Applicants refer the Examiner to *The American Heritage College dictionary* which defines "vaccine" as

> a preparation of a weakened or killed pathogen, such as a bacterium or virus, or of a portion of the pathogen's structure that upon administration stimulates antibody production against the pathogen but is incapable of causing sever infection.

Thus, Applicants assert that the term "vaccine", as used in Applicants claim, is a noun that does not require a recitation of its intended use to define its meaning. However, in the interest of advancing the prosecution of this application, Applicants have amended the preamble of claim 1 without prejudice and acquiescence.

Applicants also point out that the term fragment is not indefinite. The term as used clearly indicates that a fragment is a smaller piece of the whole. Therefore, it is readily ascertainable that Applicants refer to a piece from the whole of Streptococcal pyrogenic exotoxin B (speB). Furthermore, Applicants refer the Examiner to Figure 8 and Example 20 of the specification, which begins on page 32. In Figure 8, Applicants illustrate amino acids that are targets for mutations. Example 20 is an example of site-directed and random mutagenesis schemes. These types of methodologies were well known and utilized in the art. The Applicants remind the Examiner that the applicant need not have actually reduced the invention to practice prior to filing. *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). Thus, Applicants assert that one skilled in the art would be able to follow the guidelines established in the example of the specification to produce fragments of spe B.

In light of the above remarks, Applicants respectfully request that the § 112 second paragraph rejection be withdrawn.

35 U.S.C. § 102(a)

Claims 1-4 are rejected under 35 U.S.C. §102(a). The Office Action asserts that Applicants invention is anticipated by Kapur et al., Microbial Pathogenesis, 15:327-346, 193, ("Kapur I") and Kapur et al. PNAS, 90:7676-7680, August 1993, ("Kapur II"). Applicants respectfully request withdrawal of both Kapur references.

Applicants assert that they are two of the co-authors of the Kapur I and Kapur II cited against the present invention. Applicants submit a Declaration by Dr. James Musser (paragraphs 4 and 5), which states that the two Kapur articles describe applicants work. The Declaration further states that the Applicants are the sole inventors and that the other authors were merely working under his direction. Thus, in light of the Declaration by Dr. James Musser, Applicants have provided sufficient evidence to remove Kapur I and Kapur II. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA).

35 U.S.C. § 102(b)

Claims 1-4 are rejected under 35 U.S.C. §102(b) as anticipated by Tai et al., or Hauser and Schlievert, or Gerlach et al. The Office Action alleges that all of the references teach the present invention. Applicants respectfully traverse.

Applicants assert that none of these references teach a vaccine. Hauser and Schlievert reports a determination of the molecular weight of Group A Streptococcal infection exotoxin type B and its relationship to other pyogenic toxins and to streptococcal proteinase inhibitors. The Gerlach et al. reference presents a chemical and serological study of erythrogenic toxin type B. Tai et al. reports the complete amino acid sequence of streptococcal proteinase. Applicants respectfully assert that disclosure of a protein sequence does not anticipate the invention of a vaccine.

Applicants assert that these references are non-enabling. The reference by Tai et al. discloses an amino acid sequence that is at least 34 amino acid residues shorter than the present invention. The protein disclosed by Gerlach et al. has a different molecular weight than the present invention. Furthermore, the reference by Hauser and Schlievert, states these differences between their sequence and Gerlach and Tai. On page 4540, Hauser and Schlievert state the size difference of Gerlach and the missing amino acids of Tai. Thus, the Hauser and Schlievert reference clearly teaches against the Gerlach and Tai reference and provides evidence of these references being non-enabled. Furthermore, the sequence by Hauser has altered amino acid

sequence around the cysteine molecule, which is near the active site. This alteration was the consequence of the lack of proteolytic activity from Hauser's speB protein. Thus, this protein lacks the structural requirement to perform the protein's intended function, proteolysis (See Declaration by Dr. Musser, paragraphs 7-9). Therefore, Applicants assert that the Tai, Gerlach and Hauser references are non-enabling because they do not teach every limitation of the claimed invention. *Verdegaal Bros. v. Union Oil Co. Of California*, 814 F.2d 628,631, 2 USPQ2d (Fed. Cir. 1987). Applicants assert that the mere isolation or characterization of a protein (or its nucleic acid precursor) is insufficient to yield a vaccine. Isolation of the protein is not predictive of the likelihood of success of obtaining a functional vaccine. For example, in 1975, Tai, et. al. published an amino acid sequence of the streptococcal proteinase. However, in the nearly twenty years between 1975 and Applicants disclosure, there is no evidence of the use of cysteine protease as a vaccine against Group A Streptococcal infection. Thus, Applicants assert that the mere isolation of a protein does not equate to the success of a functional vaccine as evident by the time frame between the disclosure of the amino acid and a functional vaccine disclosed by the present invention. Therefore, the references do not contain an enabling disclosure because the public did not have complete possession of the claimed invention to combine knowledge in the art with Tai, Gerlach and Hauser references to produce the claimed invention until Applicants' disclosure. *In re Donohue*, 766 F.2d 531, 266 USPQ 6191 (Fed. Cir. 1985).

In light of the above remarks and the Declaration by Dr. Musser, Applicants respectfully request that these rejection be withdrawn.

35 U.S.C. § 103(a)

Claim 5 is rejected as unpatentable over Kapur I, or Kapur II, or Gerlach et al., or Hauser et al., or Tai et al., in view of Abe et al. Applicants respectfully assert that none of these references can be combined to teach Applicants invention.

Applicants assert that sufficient evidence has been provided in a §1.132 Declaration to remove Kapur I and Kapur II. Thus, primary references of Gerlach, Hauser, and Tai are left. Applicants have established that Gerlach, Hauser, and Tai are non-enabling due to the properties of the protein. Furthermore, Applicants have provided sufficient evidence that Hauser clearly teaches against Gerlach and Tai. Thus, Applicants assert that it is improper to combine these references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

All of these references, except for Abe et al., have already been discussed. Abe et al. does not teach using cysteine proteases as vaccines or methods of vaccination. Abe et al. discusses the toxic effect of speB toxin among others. In particular, Abe et al. discusses how speB acts as a superantigen and how this contributes to its function as a toxin. This toxic mechanism involves stimulation of immune cells that contribute to and accentuate the deleterious effects of the toxin. (*See* p.3750). This is completely unrelated to the suitability of speB as an immunizing agent. In fact, this teaching would lead one away from considering speB as a viable candidate for an immunization agent. Therefore Abe et al. could **never** be combined with another reference to yield a vaccine.

Applicants assert that the failure of these references to disclose or even suggest the use of cysteine protease as a vaccine renders their combination with any or all of the references inappropriate since there is no motivation to do so. As discussed in regards to Applicants prior arguments in this response, the mere purification and sequencing of a protein is inadequate to teach the creation of a vaccine. For example, there is no indication that the dialysis procedure described in one of the references yields a nontoxic carrier, and no indication that such compounds will yield a vaccine. In addition, the limitation that the vaccine compositions contain a physiologically acceptable vehicle in addition to the cysteine protease is ignored. Further, the claim requires that a conserved cysteine protease be present in an amount sufficient to confer immunity to group A streptococcal infection, which is the *de facto* definition of a vaccine. None of the cited references describe either the conserved cysteine protease in combination with the physiologically acceptable vehicle, or a composition comprising the conserved cysteine protease in the specified amount. These limitations are not obvious variants of the cysteine proteases described in the cited prior art. *In re Anthony*, 162 USPQ 594, 597 (CCPA 1969).

None of the references provide motivation to administer cysteine protease to a human or animal. Thus, there is no motivation in the cited prior art to incorporate the cysteine protease into pharmaceutically acceptable carriers in amounts sufficient to induce immunity against group A Streptococcal infection.

Furthermore, there is considerable evidence that Applicants invention is not obvious. Prior to Applicants invention, no one has disclosed an effective vaccine against Group A Streptococcal infection, despite the dire need to develop one. For example, rates of rheumatic fever heart disease range form 0.2 to 0.5 per 100,000 in affluent, developed communities to 125 to 960 per 100,000 in segregated, low socio-economic populations (*The Jordan Report 2000*, pp. 43-46). In the U.S., Group A Streptococcal infection causes about 25 cases of pharyngitis per

year. The grave nature of the illness caused by streptococcus coupled with the complete lack of an acceptable vaccine prior to Applicants' invention is strongly probative of nonobviousness. *In re Dow Chem. Co.*, 5 USPQ 2d 1529 (Fed. Cir. 1991) ("Recognition of need, and difficulties encountered by those skilled in the field are classical indicia of unobviousness."). Thus, Applicants respectfully request withdrawal of the 103 rejection.

35 U.S.C. § 103(a)

Claims 6-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fischetti et al. and Kehoe in view of Kapur I or II, Tai et al., Hauser et al., Gerlach et al., and further in view of Abe et al. In addition to the remarks that follow, Applicants refer the Office to arguments made earlier in this response regarding these various references.

Kapur I, Kapur II, Tai, Hauser, Gerlach, and Abe have already been discussed. The failure of Gerlach to disclose or even suggest the use of cysteine protease as a vaccine renders its combinations with any of the secondary references inappropriate. *In re Napier*, 34 USPQ 2d at 1784.

The Office Action does not point out a single suggestion to combine any of these references. The Office Action must specifically point out the suggestions to combine references, it can not merely select bits and pieces from various references and provide 20-20 hindsight recombinations to yield Applicants invention. In the instant case, even if the use of 20-20 hindsight was permitted, the references cited do not even provide the "parts" that can be combined to create Applicants invention.

Fischetti et al. can not be combined with any other reference to teach Applicants invention. Fischetti et al. constructed a vaccine virus recombinant that expressed the conserved region of the structural gene encoding the M6 molecule, which is not a cysteine protease. Kehoe is a review article that reviews prior studies related to the development of group A streptococcal vaccines *using M protein* which is different than the cysteine protease of the instant invention. Furthermore, Kehoe state that attempts to develop a Group A streptococcal infection vaccine have not been successful:

> **It may, however, be some time before an effective vaccine that could protect against a wide range of group A streptococcal M types will be produced, or even demonstrated to be feasible. It is clear that further studies are required.**

Additionally, though Kehoe may constitute an invitation to develop a Group A streptococcal infection vaccine, it fails as a §103 reference because it does not suggest the means disclosed by Applicants to accomplish that end. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

As mentioned previously, Abe et al. investigates streptococcal erythrogenic toxin **mechanisms**, therefore, it can not be combined with any other reference to yield Applicants invention.

Furthermore, Applicants assert that there is a long-felt need for the identification of an efficient streptococcus vaccine. As indicated in a 1999 article in JAMA (Vol. 281, pgs. 1973-1977), Group A streptococcus (referred to as Group A strep) is the cause of "strep throat", and it can also cause severe invasive diseases such as toxic shock syndrome, acute rheumatic fever, and others. The search for a vaccine for Group A streptococcus began in 1906 and was banned by federal law for several years after 1979, following a vaccine trial that was associated with significantly more acute rheumatic fever among vaccinated subjects. However, there still has not been an effective vaccine developed for Group A Streptococcus. In light of these comments and the Declaration (paragraph 12-13), Applicants assert that the present invention fulfills a long-felt need, a long felt need of almost a 100 years, for a vaccine that would be beneficial to humans. Thus, Applicants respectfully request that the secondary considerations of 35U.S.C. § 103 be considered.

Conclusion

In light of these remarks, Applicants respectfully request that the objections to the specification and the rejections of Applicants be reversed.

Applicants assert that in light of the above remarks, the Application is now in condition for allowance. Accordingly, Applicants respectfully request that a Letter Patent be issued on the application. If any outstanding issues remain, please contact the undersigned for quick resolution.

Applicants are filing an Information Disclosure Statement which lists all the scientific references that are cited in this response. Applicants submit these references in response to the Examiner's comments and assert that have been supplied within three months of the Office Action. Attached to this letter is a PTO form 1499 listing the scientific references as well as copies of the scientific references.

Applicants do not believe that there is a fee required to file IDS. If Applicant is in error, please charge the fee to deposit account number 06-2375/09507112 from which the undersigned is authorized to draw.

Applicants do not believe that any additional fees are due. If, however, additional fees are due, please charge the additional fees to the deposit account of Fulbright & Jaworski L.L.P., Account No. 06-2375, under Order No. 957112, from which the undersigned is authorized to draw.

Respectfully submitted,

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